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FILING DATE: *February 23, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/05616*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
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EUDES FRANCOIS MARIE	de CRECY	LA JOLLA, CA, 92037

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

CONTINUOUS CULTURE APPARATUS WITH MOBILE VESSEL, ALLOWING SELECTION OF FITTER CELL VARIANTS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 2 ☐ CD(s), Number _____

☒ Drawing(s) *Number of Sheets* 2 ☐ Other (specify) _____

☐ Application Data Sheet. See 37 CFR 1.76

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Respectfully submitted,

SIGNATURE Eudes de Crecy

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INVENTOR(S)/APPLICANT(S)

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EUDES FRANÇOIS MARIE	de CRECY	LA JOLLA, CA, 92037

Number _____ of _____

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Title: Continuous culture apparatus with mobile vessel, allowing selection of fitter cell variants.

SUMMARY

DESCRIPTION

Continuous culture vessels have been used since the 1950's to select for cells that have a higher proliferation rate under given conditions (Monod J., 1950, Ann. Inst. Pasteur. 19:390-410; Novick A., Szilard L., 1950, Science 112:715-716). The power of these devices have never been used to their fullest because they positively select mutants that evade dilution, primarily through attachment to vessel surfaces, resulting in persistent sub-populations of uncontrollable size and growth rate.

One possible solution to overcome this drawback is the implementation of a device with two growth chambers periodically undergoing transient phases of sterilization as described in the patent by Marliere and Mutzel (1999, DE2982162U1).

The solution described in this application is radically different as it consists of using a mobile vessel around the solution instead of moving the solution from one chamber to another.

More specifically, the vessel consists of a sterile flexible tube containing the culture media.
A portion of this tube that can be physically and temporarily separated from the rest of the tube by some lock devices, will contain the cell culture, and will be designated therein as the culture vessel. Fresh medium will be periodically added to the culture by sliding a portion of medium filled tubing.

The design of the lock, see figure, will drive the amount of medium that will be added at each sliding cycle.

Spend culture and medium will also be eliminated through a tubing sliding step.

The frequency of the movement of the tube can be set by the experimenter reproducing a chemostat regime or can be for example regulated through a feedback loop depending on the turbidity of the culture in the vessel that will be read via a turbidometer, emulating a turbidostat regime. Other regulation approaches can be implemented.

The system is designed to allow the complete rotation of the vessel and the locks.

The positioning of the vessel will be adjusted in accordance to the aeration cycle.

Aeration can be provided two ways:

1- by passive diffusion of ambient air through gas permeable tubing,
2- by injecting filtered air that will first bubble through the media and then be introduced in the vessel through the entrance locking sub-system.

Previously the spend air will have been eliminated by rotation of the vessel in the upright position as described in attached figures.

The presence of several gates (superior to 2) should avoid any contamination in the tubing of the medium in the up chamber tubing. However several UV gates can be added upstream and downstream of the culture vessel for additional security.

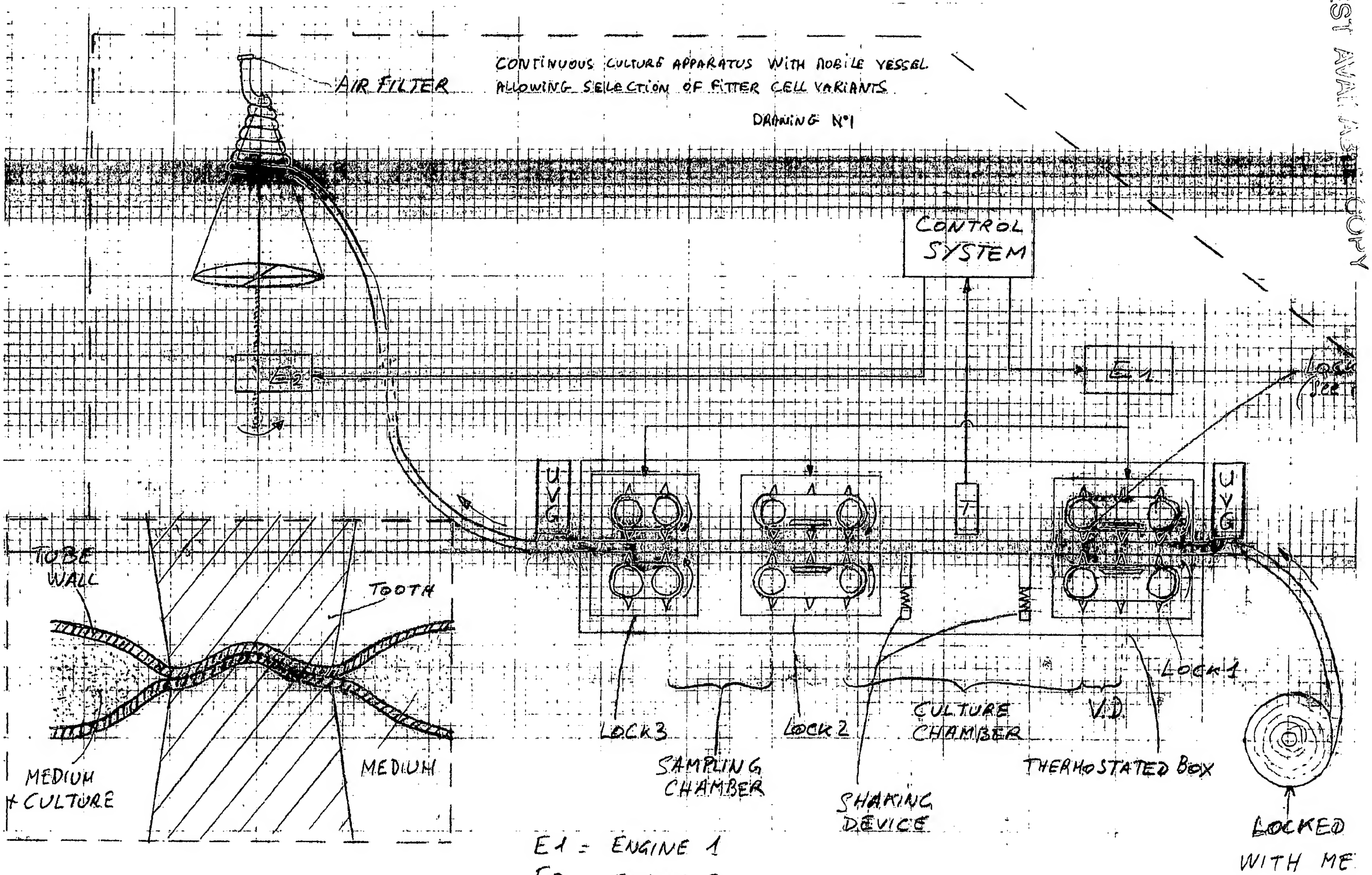
Inoculation will be performed by sterily injecting a cell culture through the lower lock that would have been set in the opened position.

An added lock will eventually be added downstream of the chamber lock to create a sampling chamber.

Tubing specifications: The tubing must be large enough to avoid capillarity problems that would prevent the air from circulating freely. The tubing should sustain sterilization cycle, be gas permeable, be flexible enough to be closed by compression and be clear enough to allow any optical measurement.

CONTINUOUS CULTURE APPARATUS WITH MOBILE VESSEL ALLOWING SELECTION OF FITTER CELL VARIANTS

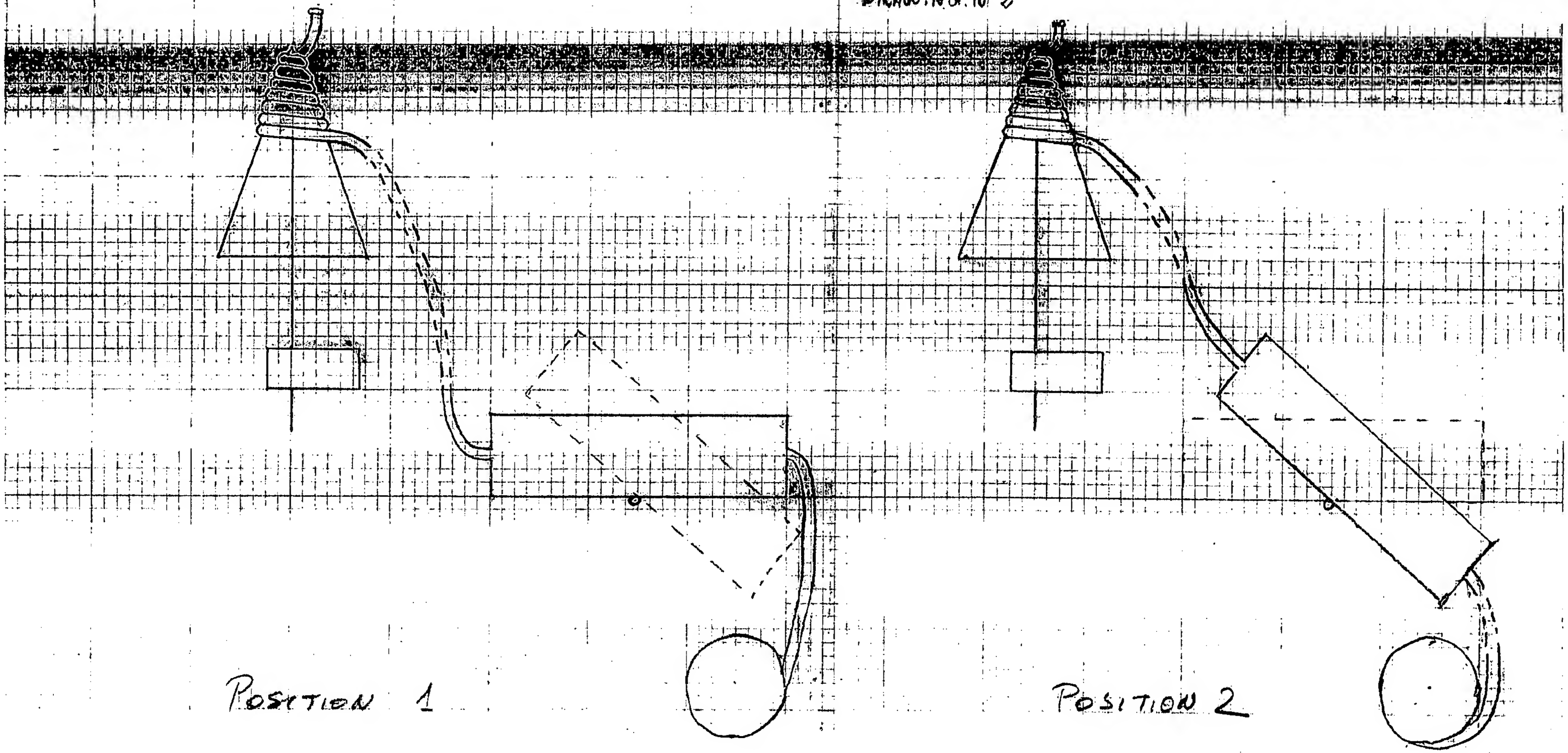
DRAWING N°1



LOCK TOOTH DETAIL

E1 = ENGINE 1
E2 = ENGINE 2
T = TURBIDOMETER
UVG = ULTRA-VIOLET GATE
V.D. = VOLUME OF DILUTION

DRAWING N° 2



POSITION 1

POSITION 2